ANNEX G TO DOD SMALLPOX RESPONSE PLAN 14 June 2002
MEDICAL CARE OF SMALLPOX PATIENTS (VARIOLA INFECTION).

REFERENCES.

a. CDC Interim Smallpox Response Plan, Annex 1. Overview Of Smallpox, Clinical Presentations, and Medical Care of Smallpox Patients. http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/.

b. United States Army Medical Command. How-To" Guide for Command Surgeons: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

c. United States Army Medical Command. "How To" Guide for Unit Leaders and Unit Health Care Providers: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

d. United States Army Medical Command. "How To" Guide for Investigational New Drug (IND) Protocols, Supplement: Cidofovir (Vistide®, Gilead) to Treat Variola Infection (IND # pending). Falls Church, VA, publication pending.

e. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002; 346:1300-8. http://content.nejm.org/cgi/reprint/346/17/1300.pdf.

f. Army Regulation 40-535, Air Force Regulation 164-5, OPNAVINST 4630.9C, MCO P4630.9A. Worldwide Aeromedical Evacuation. 10 May 1979. http://www.usapa.army.mil/pdffiles/r40_535.pdf.

1. General. This DoD Annex augments CDC Annex 1 (reference a). Appendix G-1 summarizes CDC Annex 1 and this DoD Annex on one page.

a. Mission. Health-care workers will render supportive and life-sustaining care to treat patients diagnosed with smallpox (variola infection).

b. Assumptions.

(1) Although smallpox spreads widely across human populations, control measures will eventually slow and then stop epidemic spread. Depending upon the method, extent, and duration of smallpox transmission, restriction and control of the ensuing epidemic will be effective.

(2) Variola infection is not inevitably fatal. About 70% of unvaccinated people will survive, as will 97% of vaccinated people. Adequate medical support may raise this figure.

The existence of a possible specific treatment for the disease, the investigational antiviral medication cidofovir (*Vistide*, Gilead Sciences, www.gilead.com/wt/sec/vistide), may increase the cited survival probabilities.

(3) The US Army Medical Research & Materiel Command (USAMRMC) is applying to the Food & Drug Administration (FDA) for permission to use cidofovir (*Vistide*, Gilead Sciences) under an investigational new drug (IND) protocol to treat human variola infections. After meeting regulatory requirements, FDA will approve this IND protocol.

c. Planning Factors.

(1) Disease Progression. Appendix G-2 outlines the clinical development of variola infection (smallpox). Medical management of a patient with smallpox is mainly supportive.

(2) Clinical Care. Good care consists of (a) isolation of the patient to prevent transmission of the smallpox virus to non-immune people, (b) monitoring and maintaining fluid and electrolyte balance, (c) skin care, and (d) monitoring for and treatment of complications. Unless the diagnosis of smallpox is laboratory confirmed, vaccinate the patient if he or she will be isolated with other confirmed or suspected smallpox cases. Vaccination of suspected cases of smallpox is done to prevent the accidental transmission of smallpox virus to any suspected smallpox patients who have been misdiagnosed as smallpox cases. See also Appendix G-3.

(3) Education and Awareness. Education and training of treatment teams (T-Teams) must occur before a smallpox outbreak occurs. The education of healthcare providers of all specialties about the existence of treatment teams will be necessary for timely alert and communication. Informing the military leadership and the public about these T-teams will aid morale.

(4) Access to Cidofovir.

(a) MTFs will not use on-hand stocks of cidofovir to treat patients infected with variola virus, nor order cidofovir from other sources, without first coordinating with the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

(b) USAMRIID will establish a common point of access for telephonic requests for use of cidofovir for a named patient by a physician willing to comply with IND requirements (references b, c, and d). Access to cidofovir for eligible patients will be facilitated by regional treatment teams (T-Teams). Civilian healthcare providers should contact the CDC Drug Service for VIG or cidofovir: CDC Drug Service, National Center for Infectious Diseases, Mail stop D-09, Atlanta, GA 30333; 404-639-3670, fax 404-639-3717.

(5) Training. Treatment teams will be trained in the requirements of IND protocols in general and the cidofovir treatment protocol in particular, to allow prompt use of this agent. USAMRMC and USAMRIID will coordinate such training.

(6) Personnel Resources. MTF commanders will develop procedures for emergency credentialing of healthcare workers to assist with disease outbreaks. The specialized treatment team will travel to the MTF with the smallpox patients. The gaining MTF will assign additional personnel to the treatment team, as requested by the treating physician(s). Additional DoD assets will be assigned, if requirements extend beyond the capabilities of the local MTF.

(7) Other Medications. If therapy with cidofovir is ineffective, clinicians may be inclined to try other therapeutic modalities unavailable when routine smallpox vaccinations ceased in the 1970s and 1980s (e.g., interferons, other antivirals). Little or no data may exist to support the safety or effectiveness of such approaches and no Federal agency sanctions their use. Nonetheless, DoD clinicians reserve their individual prerogatives and responsibilities in the clinical practice of medicine for individual patients.

d. Coordinating Instructions.

(1) Command Relationships. The treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

(2) Communication. No information will be conveyed to other external sources, including the media, without command approval. If working in coordination with local treatment teams, no information will be conveyed to other external sources, including the media, without approval of, or simultaneous presentation with, the coordinating agency (CONUS--CDC, OCONUS--WHO).

e. Legal Considerations.

(1) All use of IND agents will be performed in accordance with IRB-approved guidelines and FDA regulations (see references b, c, and d, and Appendix G-4). MTFs will provide personnel and supply resources to the treatment teams to satisfy regulatory requirements.

(2) Smallpox outbreaks may occur OCONUS. Travel of personnel into or out of the involved region may become difficult or impossible, for medical, legal, or political reasons. US unified commands will provide access by treatment teams to patient needing treatment, as well as security for these T-Teams.

2. Execution.

a. Concept of Operations. Cidofovir is a medication licensed by the FDA for treatment of cytomegalovirus (CMV) retinitis in people infected with the human immunodeficiency virus (HIV) [see Appendix H-3]. For a different use, cidofovir is an investigational, moderately toxic antiviral agent projected to be given intravenously once a week in the treatment of variola infection. Side effects, especially renal insufficiency, occur. Animal-

challenge experiments show the efficacy of cidofovir against orthopoxviruses (the group of viruses that includes variola and vaccinia viruses). It is presently unknown whether cidofovir will be effective in treating human smallpox infection.

(1) Cidofovir must be administered by an FDA-registered principal investigator or subinvestigator. Patient consent must be obtained before administration. See also Appendix G-4, for exceptions for unconscious patients.

(2) Because of the administrative burden of implementing an IND protocol, and this drug's intravenous route of administration, multidisciplinary treatment teams will be assembled to travel to areas affected by an outbreak, to administer cidofovir and assist with patient care. Prior vaccination against smallpox will be a condition of membership on these teams. Such T-Teams will include:

(a) Team leader – Senior medical officer.

(b) One or more infectious disease or dermatology physicians.

(c) One or more intensive-care physicians.

(d) Pharmacy officer and technician.

(e) Laboratory officer and technician.

(f) Nursing support – Two or more ICU-trained nurses.

(g) Preventive-medicine/Occupational-health specialist (physician or senior technician)

(h) Preventive-medicine technician

(i) Communications specialist

(3) Actual use of cidofovir under the FDA-approved protocol is specified within the treatment protocol (reference d). This protocol addresses dosage, expected side effects, physiologic and laboratory monitoring, and regulatory and reporting issues.

(4) The treatment of smallpox will occur within local medical facilities. Evacuation of smallpox patients will be avoided or minimized, to reduce contact with the patient and further spread of disease.

(5) Smallpox patients will be hospitalized, if adequate facilities permit. Adequate infection-control procedures (Annexes C and G) will be paramount. Negative airflow rooms are warranted. Cohorting (i.e., sharing of rooms/facilities by patients with similar disease categories) is recommended. Given adequate medical observation (at least daily

physician visits) and restriction of further exposures, minimal care or out-of-hospital care is possible.

b. Tasks and Responsibilities.

(1) Identification and specific diagnosis of patients with smallpox will be the responsibility of healthcare providers at the MTF level, in consultation with regional infectious-diseases, dermatology, and pathology specialists, as needed. MTFs will make every attempt, using organic assets, to exclude the more common and probable diagnoses (e.g., chickenpox, allergic reactions, insect bites), using the CDC Generalized Vesicular or Pustular Rash Illness Protocol. See Annex A for the sequence when initiating an alert to the possible presence of a patient with smallpox.

(2) Once a definite or probable diagnosis of smallpox has been made, attending physicians will consider whether cidofovir treatment may be appropriate, consulting with local or regional infectious-disease (ID) or dermatology physicians. The physicians may request use of cidofovir for a named patient by telephoning USAMRIID at 1-800-USA-RIID [after duty hours, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-619-6092]. USAMRIID will coordinate with treatment teams, which will travel to the MTF caring for the diagnosed smallpox patient. These teams will be responsible for the treatment of patients with the indicated medications. IND-specific procedures will be followed carefully.

(3) The MTF will provide routine medical care in accordance with standard practice, with laboratory, radiology, and pathology support. If the patient is treated with cidofovir, the treating team will have responsibility for the completion and maintenance of records and reports, and the processing or packaging of pathologic or autopsy materials.

(4) MTF commanders will be responsible for transporting patients between MTFs; provision of ancillary supply and personnel resources to treatment teams; pharmacy and laboratory support; and communication support.

(5) The service member's unit will be responsible for initial transportation to the first-level MTF. Once within the medical system, it will be the responsibility of the medical-evacuation system for further patient transportation as needed. Evacuation of smallpox patients will be avoided or minimized, to reduce contact with the patient and further spread of disease.

c. Reporting.

(1) T-team leaders will periodically brief the MTF commander on the status of patients with smallpox, at a frequency directed by the commander. Similar briefings will occur for and at the direction of the commander, USAMRIID.

(2) IND protocol reports will be submitted as detailed in reference d.

3. Operational Constraints.

a. Equipment. MTFs caring for smallpox patients can be expected to provide care up to and including intensive-care support. MTFs may expect this requirement to include appropriate equipment (e.g., ventilators, dialysis machines) and pharmacy support (e.g., vasopressors, and routine antibiotics).

b. Training. T-Teams will be trained in the use and monitoring of therapy with cidofovir. USAMRMC and USAMRIID will coordinate such training. Periodic alert exercises, without travel, will be performed at least quarterly to sustain team proficiency.

c. Control of IND Agents. MTF pharmacy support to treatment teams will include storage (see below), control, and security for both cidofovir and locally available medications. Pharmacy assets on the treatment teams will prepare and dispense cidofovir for the treatment team's use. Emergency use of an investigational drug for a named patient will comply with notification requirements to U.S. Army Medical Command, in accordance with Army Regulation 40-7 (Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances, 4 January 1991), paragraph 4-9, and comparable regulations in other military Services.

d. Security. MTFs will coordinate with local military and local law enforcement personnel to protect patients, medical personnel, and the IND medications.

e. Surge Capacity. Depending on the size of the smallpox outbreak, the number of people infected with smallpox may exceed the ability of treatment teams to care for those infected with smallpox. Augmentation of T-Teams may occur by one or more of the following:

(1) Assignment of one or more additional regional treatment teams by USAMRIID, to the affected MTF or area;

(2) Augmentation of the team by local physician, pharmacy, nursing, and laboratory assets, with oversight of cidofovir administration remaining under the purview of the initial team's subinvestigators; or

(3) Coordination with local civilian response teams, as needed. See paragraph 5 below.

4. Administration and Logistics.

a. Shipping and Distribution. Either the T-Teams will transport the cidofovir themselves, or they will coordinate with the US Army Medical Materiel Agency (USAMMA) for transportation (see Annex I).

b. Supply and Storage. Supplies of cidofovir, delivered from USAMRIID, will be stored and maintained by the MTF pharmacy under the appropriate room-temperature conditions (reference d).

c. MTFs will provide administrative support for protocol performance by the treatment teams (e.g., office space, copying, automation, communication support).

5. Special Situations.

a. Treatment of Military Beneficiaries in CONUS. Military personnel and beneficiaries in CONUS will receive treatment in local military MTFs. Infection-control principles call for patients with smallpox to be cared for in designated Type-C treatment facilities. See also Annex C. At the beginning of a smallpox outbreak, this would likely be the first hospital(s) to which such patients are admitted.

b. Relation to Civilian Facilities. Members of DoD treatment teams will probably not be licensed under state regulations to provide medical care outside of a federal MTF. State regulations may be waived in time of emergency. Cidofovir and other IND medications may not be shared with or diverted to people not registered under the protocol, without the detailed knowledge and explicit agreement of USAMRIID and the principal investigator (who may also need FDA agreement).

c. Treatment of Military Beneficiaries Outside of CONUS. Military personnel and beneficiaries OCONUS will receive treatment in local MTFs. Members of DoD treatment teams will probably not be licensed, by national laws or regulations, to provide medical care outside of the military MTF. These laws and regulations may be waived in time of emergency. Local civilian MTFs may provide care to military beneficiaries under applicable Status of Forces Agreements or other agreements. Cidofovir and other IND medications may not be shared with or diverted to people not registered under the protocol, without the detailed knowledge and explicit agreement of USAMRIID and the principal investigator (who may also need FDA agreement).

d. Treatment of Military Beneficiaries in Transit. If a patient started on cidofovir at one MTF is transferred to another medical facility, a physician at the gaining institution may continue cidofovir administration only if he or she agrees to join the IND protocol as a subinvestigator and takes responsibility for fulfilling FDA regulations for conducting an FDA-approved IND protocol.

APPENDIX G-1
Medical Care Of Smallpox Patients (Variola Infection) – Summary.

1. Smallpox (variola infection) is not inevitably fatal. About 70% of unvaccinated people will survive infection, as will 95% of vaccinated people. The existence of a possible specific treatment for the disease, cidofovir (*Vistide*, Gilead Sciences), may increase survival.

2. The US Army Medical Research & Materiel Command (USAMRMC) is applying to the Food & Drug Administration (FDA) for permission to use cidofovir (*Vistide*, Gilead Sciences) under an investigational new drug (IND) protocol to treat human variola infections. This annex assumes FDA will approve this IND protocol.

3. Because of the administrative burden of implementing an IND protocol, and this drug's intravenous route of administration, multidisciplinary treatment teams will be assembled to travel to areas affected by a smallpox outbreak, to administer cidofovir and assist with patient care. Prior vaccination against smallpox will be a condition of membership on these teams.

4. Once a definite or probable diagnosis of smallpox has been made, attending physicians will consider whether cidofovir treatment may be appropriate, consulting with local or regional infectious-disease (ID) or dermatology physicians. The physicians may request use of cidofovir for a named patient by telephoning USAMRIID at 1-800-USA-RIID. After duty hours, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-619-6092.

5. USAMRIID will coordinate with these treatment teams (T-teams), which will travel to the MTF caring for the diagnosed smallpox patient. IND-specific procedures will be followed carefully. The treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

6. Treatment team leaders will periodically brief the MTF commander on the status of patients with smallpox, at a frequency directed by the commander. Similar briefings will occur for and at the direction of the commander, USAMRIID. Treatment team leaders and IND investigators will submit IND protocol reports as required by the FDA.

APPENDIX G-2
Stages of Smallpox Infection.

| Communic-ability | Exposure = Day 0 | Symptoms | Day of Symptoms | Disease Progress |
|---|---|---|---|---|
| Not contagious | Day 1 | No symptoms | | Virus introduced to respiratory Tract |
| | 2 | | | |
| | 3 | | | |
| | 4 | | | Virus appears in lymph nodes |
| | 5 | | | |
| | 6 | | | Virus replicates in lymph System |
| | 7 | | | |
| | 8 | | | |
| | 9 | | | |
| | 10 | | | |
| | 11 | | Day 1 | |
| | 12 | First symptoms | 2 | Fever, backache, headache, nausea, malaise, enanthem |
| | 13 | | 3 | |
| Contagious | 14 | | 4 | |
| | 15 | Rash | 5 | Macules (spots) |
| Very contagious | 16 | | 6 | Papules (bumps, pimples) |
| | 17 | | 7 | |
| | 18 | | 8 | |
| | 19 | | 9 | Vesicles (blisters) |
| | 20 | | 10 | |
| Contagious | 21 | | 11 | Pustules (pus-filled Blisters) |
| | 22 | | 12 | |
| | 23 | | 13 | |
| | 24 | | 14 | |
| | 25 | | 15 | Scabs |
| Scabs contagious | 26 | | 16 | |
| | 27 | | 17 | |
| | 28 | | 18 | |
| | 29 | | 19 | |
| | 30 | | 20 | |
| Not contagious | 31 | | | Scars |
| | 32 | | | |

*

Adapted from Fenn (2001, p.19), Breman & Henderson (2002), and Fenner et al. (1988).

Note: First symptoms may begin as soon as 7 days after exposure or as late as 17 days after exposure.

APPENDIX G-3
Considerations in Clinical Care of Variola Infection.

1. Fluid and Electrolyte Balance. During the vesicular and pustular stages of smallpox, patients may experience significant fluid losses and become hypovolemic or develop shock. Fluid loss can result from (a) fever, (b) nausea and vomiting, (c) decreased fluid intake due to swallowing discomfort from pharyngeal lesions, (d) body fluid shifts from the vascular bed into the subcutaneous tissue, and (e) massive skin desquamation in patients with extensive confluent lesions. Electrolyte and protein loss may also occur in these patients. Monitor fluid and electrolyte balance in hospitalized patients with appropriate oral or intravenous correction of imbalances. Encourage patients with less severe disease who do not require hospitalization to maintain good oral intake of fluids, educated on the signs/symptoms of hypovolemia/dehydration, and counsel them on when to seek medical attention if hypovolemia/dehydration occurs.

2. Skin Care. Keep the skin clean. Avoid rupturing vesicles or pustules. Do not apply salves or ointments. In general, allow scab lesions to heal and separate on their own. All scabs should separate by 3 to 4 weeks. But lesions on the palms and soles may persist longer than 3 to 4 weeks unless artificially removed. Bacterial superinfection of lesions may occur and should be treated with appropriate antibiotics.

3. Monitoring and Treatment of Complications. Several types of complications may occur during the course of a smallpox infection. These include: (a) hemorrhagic, (b) secondary bacterial infections, (d) corneal ulceration and/or keratitis, (d) arthritis or osteomyelitis variolosa, (e) respiratory, (f) encephalitis, (g) gastrointestinal, and (h) genitourinary. These complications and their treatment are described below.

a. Hemorrhagic. Minor hemorrhagic manifestations such as subconjunctival hemorrhages occur commonly in smallpox patients. If subconjunctival hemorrhages are isolated and not accompanied by consumption coagulopathy or active bleeding (e.g., decreasing hemoglobin, hematocrit, or platelets), no specific therapy is needed. However, if signs of more extensive hemorrhage are present (e.g., mucosal bleeding, bleeding into smallpox lesions, ecchymoses, hematemesis, hematuria), evaluate the patient for disseminated intravascular coagulation (DIC) and treat appropriately. Hemorrhagic complications may indicate a more severe form of the disease called hemorrhagic smallpox, which has a poor prognosis. Because of a high, sustained viremia coupled with mucosal hemorrhaging, these patients are highly infectious.

b. Secondary Bacterial Infections. Bacterial superinfections can include abscesses of skin lesions, pneumonia, osteomyelitis, joint infections, and septicemia. Perform laboratory diagnostics to help guide antibiotic therapy.

c. Corneal Ulceration and/or Keratitis. These complications occurred more frequently in hemorrhagic-type smallpox but were occasionally seen in the more typical ordinary-type

smallpox. In a case series reported by Rao from Bombay in 1972, corneal ulcers occurred in 1% of non-hemorrhagic type smallpox cases and keratitis occurred in 0.25%. Corneal ulcerations can appear around the second week of illness and begin at the corneal margins. Ulcers can heal rapidly, leaving a minor opacity, or on occasion, may cause severe corneal scarring. Keratitis and corneal ulceration was far more common in malnourished individuals. Topical idoxuridine has been used but its efficacy is undocumented.

d. Arthritis or Osteomyelitis Variolosa. This complication occurred in 1.7% of the cases in the Rao case series. It usually occurred after the 15$^{th}$ day, accompanied by a brief recurrence of fever during scabbing. The elbow is the most commonly affected joint. Symmetrical, bilateral involvement was frequently seen. This complication was most commonly due to viral infection of the metaphyses of growing bones. Most cases resolved without permanent deformity.

e. Respiratory. Viral bronchitis and pneumonitis can be common complications of severe smallpox. Treatment is symptomatic, treating hypoxemia with oxygen and/or intubation/ventilation as indicated. Secondary bacterial pneumonia can occur and should be treated with appropriate antibiotics as guided by laboratory diagnostics. Pulmonary edema is common in more severe forms of smallpox (i.e., hemorrhagic, flat-type), and should be treated with careful monitoring of oxygenation, fluid status, and blood pressure, with supplemental oxygen and diuretics administered as needed. Patients with cough during the first week of disease may transmit disease more readily than patients without cough. Patients who developed a cough after symptom day 10, when viral counts in secretions were lower, were not as infectious as those who developed coughs earlier.

f. Encephalitis. This complication occurred in about one out of every 500 cases of smallpox. It usually appeared between the sixth and tenth day of illness, when the rash was still in the papular or vesicular stage. During the smallpox era, this complication was a minor contributor to the case-fatality rate of variola major. Although sometimes slow, recovery was usually complete.

g. Gastrointestinal – Nausea and vomiting can occur in the earlier stages of smallpox, especially in the prodromal period before rash development and should be treated symptomatically. Diarrhea may occasionally occur in the prodromal period or in the second week of illness and should also be treated symptomatically. Acute distension of the stomach occurred rarely and was more common in infants. In some severe cases of smallpox (especially flat-type), extensive viral infection of intestinal mucosa occurred with sloughing of the mucosal membrane. Most of these cases were fatal.

h. Genitourinary System. Orchitis occurred in 0.1% of the Rao case series and was usually unilateral. Hematuria can be present in hemorrhagic type smallpox if bleeding into the pelvis of the kidney occurs.

4. For additional advice, seek appropriate medical consultations.

APPENDIX G-4
Exceptions to General Rule to Obtain Informed Consent for Unconscious or Incapacitated Patients.

1. PURPOSE. To describe conditions within federal regulation that provide for exceptions to the general requirement to obtain individual informed consent before use of investigational new drugs (IND).

2. FACTS.

a. Under normal circumstances, DoD health-care providers will obtain documentation of the individual informed consent of the recipients of investigational new drugs (INDs), under provisions of Title 21 Code of Federal Regulations (CFR) Section 50.20, 21 CFR 312, DOD Directive 3216.2 (Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research), and related regulations.

b. Under unusual circumstances, such as on a battlefield, it may not be possible to obtain consent in this way. Individuals incapable of reaching their own reasoned decision on whether or not to grant consent include people incapacitated physically or mentally, such as people who are unconscious.

c. Title 21 CFR 50.23 specifies conditions for exception from the general requirement to obtain consent. Both the protocol investigator and a physician not otherwise participating in the IND protocol must certify in writing all the following:

(1) The human subject is confronted by a life-threatening situation necessitating the IND drug,

(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject,

(3) Time is not sufficient to obtain consent from the subject's legal representative, and

(4) There is no alternate method of approved or generally recognized therapy providing an equal or greater likelihood of saving the life of the subject.

d. If time is not sufficient to permit the physician not participating in the clinical investigation to render a review, it shall be made within 5 working days after use of the drug.

e. Title 10 United States Code (USC) Section 980 prohibits DoD research unless "the informed consent of the subject is obtained in advance" or "in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance." This law does not apply to the

situation of individuals described in paragraphs 2b and 2c above, because the use of the IND drug would be for a treatment purpose and with individual life-saving intent, rather than as a function of a "research" undertaking within the meaning of 10 USC 980. This understanding of 10 USC 980 is supported by applicable case law (*Doe v. Sullivan*, 756 F. Supp. 12 (DDC 1991), affirmed, 938 F.2d 1370 (CADC 1991)).

f. Title 10 USC 1107 and 21 CFR 50.23(d) establish rules for waiver of informed consent by the President for IND drug use in particular military operations. As indicated in the legislative history of 10 USC 1107, these requirements for a Presidential waiver are not applicable to standard medical practice in the United States, such as authority to provide life-saving treatment to unconscious or incapacitated patients.

g. Title 21 CFR 50.24 discusses exception from informed-consent requirements for research of emergent conditions where it is anticipated that subjects will not be able to give their informed consent as a result of their medical conditions. In other words, 21 CFR 50.24 addresses situations where a large fraction of subjects will be unable to provide consent. This situation is not currently anticipated for any IND drug under evaluation by the Department of Defense.